IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Salama et al.	)	Atty. Dkt. 7014-220
	)	
Appl. No.: **National Stage of PCT/DE2003/004211**	)	
	)	Examiner: n/a
	)	
Filed: herewith	)	Group Art Unit: n/a

For: **Proline derivatives used as pharmaceutical active ingredients for the treatment of tumors**

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please amend the above-identified application as set forth below.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 9 of this paper.

Remarks begin on page 18 of this paper.

Amendments to the Specification:

On page 1, between line 5 and 6, directly after the title, please insert the following paragraph:

-- This is the U.S. national stage of International application **PCT/DE2003/004211**, filed December 18, 2003 designating the United States. --.

On page 1, please delete line 8.

On page 1, between lines 9 and 10, please insert:

-- FIELD OF THE INVENTION --.

On page 1, between lines 17 and 18, please insert:

-- BACKGROUND OF THE INVENTION --

On page 2, between lines 23 and 24, please insert the following new heading and subsequent paragraphs:

-- SUMMARY OF THE INVENTION

Please amend the paragraph stating on page 7, line 18 as follows:

-- Preferably, 4-hydroxyproline ethyl ester, 4-hydroxy-1,1-dimethylproline ethyl ester iodide, 4-hydroxyproline isobutyl ester, 4-hydroxy-1,1-dimethyl proline isobutyl ester iodide, 4-hydroxy-1-cyclohexylproline isobutyl ester, 4-hydroxy-1-diphenylmethylproline isobutyl ester hydrobromide, 4-hydroxy-1-methylproline, 4-hydroxy-1-methylproline

ethyl ester, 4-hydroxy-1-methylproline isobutyl ester, 1-methyl-4-phenylaminocarbonyloxyproline, 1-methyl-4-phenylaminocarbonyloxyproline isobutyl ester, (R)-(+)-α,α-diphenyl-2-pyrrolidinemethanol and/or (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol are employed in diagnosis, prophylaxis, follow-up, therapy and/or aftercare of diseases associated with cell growth, cell differentiation and/or cell division, especially tumors. The respective dose or dose range for administering the pharmaceutical agent of the invention is in an amount sufficient to achieve the desired prophylactic or therapeutic antiviral effect. The dose should not be selected in such a way that undesirable side effects would dominate. In general, the dose will vary with the age, constitution, sex of a patient, and obviously with respect to the severity of a disease. The individual dose can be adjusted both with respect to the primary disease and with respect to ensuing additional complications. The exact dose can be detected by a person skilled in the art, using well-known means and methods, e.g. by determining the size of the tumor, the number of leukocytes or the like as a function of the dosage or as a function of the vaccination scheme or of the pharmaceutical carriers and the like. Depending on the patient, the dose can be selected individually. For example, a dose of pharmaceutical agent just tolerated by a patient can be one where the local level in plasma or in individual organs ranges from 0.1 to 100,000 µM, preferably between 1 and 1,000 µM. Alternatively, the dose can also be estimated relative to the body weight of the patient. In this event, for example, a typical dose of pharmaceutical agent would be adjusted in a range of more than ~~0.1 g~~ 0.1 mg per kg body weight, preferably between 0.1 and ~~5,000 g/kg~~ 5,000 mg/kg. Furthermore, it is also possible to determine the dose with respect to individual organs rather than the overall patient. For example, this would apply to those cases where the pharmaceutical agent of the invention, incorporated in the respective patient e.g. in a biopolymer, is placed near particular organs by means of surgery. A number of biopolymers capable of liberating the molecules in a desired manner are well-known to those skilled in the art. For example, such a gel may include from 1 to ~~1000 g~~ 1000 mg of compounds or pharmaceutical agent of the invention per ml gel composition, preferably between 5 and ~~500 g/ml~~ 500 mg/ml, and more preferably between 10 and ~~100 g/ml~~ 100 mg/ml. In this event, the therapeutic agent will be administered in the form of a solid, gel-like or liquid composition. --

Please amend the paragraph starting on page 9, line 1 as follows:

-- In addition to the above-specified concentrations during use of the compounds of the invention, the compounds in a preferred embodiment can be employed in a total amount of 0.05 to ~~500 g/kg~~ 500 mg/kg body weight per 24 hours, preferably 5 to ~~10 g/kg~~ 10 mg/kg body weight. Advantageously, this is a therapeutic quantity which is used to prevent or improve the symptoms of a disorder or of a responsive, pathologically physiological condition. The amount administered is sufficient to prevent or inhibit growth, metastasization, invasion, infiltration or angiogenesis of the tumor. With respect to their prophylactic or therapeutic potential, the effect of the compounds of the invention on the above tumors is seen e.g. as an inhibition of growth or other. For example, the therapeutic effect can be such that, as a desirable side effect, particular anti-tumor medicaments are improved in their effect or, by reducing the dose, the number of side effects of these medicaments will be reduced as a result of applying the compounds of the invention. Of course, the therapeutic effect also encompasses direct action on the tumor. That is, however, the effect of the compounds of the invention is not restricted to eliminating tumors, but rather comprises the entire spectrum of advantageous effects in prophylaxis and therapy. Obviously, as set forth above, the dose will depend on the age, health and weight of the recipient, degree of the disease, type of required simultaneous treatment, frequency of the treatment and type of the desired effects and side-effects. The daily dose of 0.05 to ~~500 mg/kg~~ 500 mg/kg body weight can be applied as a single dose or multiple doses in order to furnish the desired results. The dose levels per day can be used in prevention and treatment of a tumor disease. Typically, pharmaceutical agents in particular are used in about 1 to 15 administrations per day, or alternatively or additionally as a continuous infusion. Such administrations can be applied as a chronic or acute therapy. Of course, the amounts of active substance that are combined with the carrier materials to produce a single dosage form may vary depending on the host to be treated and on the particular type of administration. In a preferred fashion, the daily dose is distributed over 2 to 5 applications, with 1 to 2 tablets including an active substance content of 0.05 to ~~5 g/kg~~ 5 mg/kg body weight being administered in each

application. Of course, it is also possible to select a higher content of active substance, e.g. up to a concentration of ~~500 g/kg~~ 500 mg/kg. For example, the tablets can also be sustained-release tablets, in which case the number of applications per day is reduced to 1 to 3. The active substance content of sustained-release tablets can be from 3 to ~~300 g~~ 300 mg. If the active substance - as set forth above - is administered by injection, the host is preferably contacted 1 to 8 times per day with the compounds of the invention or by using continuous infusion, in which case quantities of from 1 to ~~400 mg~~ 400 mg per day are preferred. The preferred total amounts per day were found advantageous both in human and veterinary medicine. It may become necessary to deviate from the above-mentioned dosages, and this depends on the nature and body weight of the host to be treated, the type and severity of the disease, the type of formulation and application of the drug, and on the time period or interval during which the administration takes place. Thus, it may be preferred in some cases to contact the organism with less than the amounts mentioned above, while in other cases the amount of active substance specified above has to be surpassed. A person of specialized knowledge in the art can easily determine the optimum dosages of active substance required in each case and the type of application of the active substances. In another particularly preferred embodiment of the invention, the compounds of the invention or the pharmaceutical agents are used in a single administration of from 1 to 80, especially from 1 to ~~30 g/kg~~ 30 mg/kg body weight. In the same way as the total amount per day, the amount of a single dose per application can be varied by a person of specialized knowledge in the art. Similarly, the compounds used according to the invention can be employed in veterinary medicine with the above-mentioned single concentrations and formulations together with the feed or feed formulations or drinking water. A single dose preferably includes that amount of active substance which is administered in a single application and normally corresponds to one whole, one half daily dose or one third or one quarter of a daily dose. Accordingly, the dosage units may preferably include 1, 2, 3 or 4 or more single doses or 0.5, 0.3 or 0.25 single doses. In a preferred fashion, the daily dose of the compounds according to the invention is distributed over 2 to 10 applications, preferably 2 to 7, and more preferably 3 to 5 applications. Of course, continuous infusion of the agents according to the invention is also possible.--

On page 13, please amend the paragraph starting on line 27 as follows:

-- In a preferred fashion the pharmaceutical agent may further include one or more additional agents from the group of antiviral, fungicidal or antibacterial agents and/or immunostimulators or chemotherapeutic agents. Preferably, the antiviral agents are protease inhibitors and/or reverse transcriptase inhibitors. The immunostimulators are preferably bropirimine, anti-human alpha-interferon antibodies, IL-2, GM-CSF, interferons, diethyl dithiocarbamate, tumor necrosis factors, naltrexone, tuscarasol and/or rEPO. The chemotherapeutic agents are preferably alitretinoin, aldesleukin (IL-2), altretamine, all-*trans*-retinoic acid (tretinoin), aminoglutethimide, anagrelide, anastrozole, asparaginase (*E. coli*), azathioprine, bicalutamide, bleomycin, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine (2-CDA), cyclophosphamide, cytarabine, dacarbazine, dactinomycin D, daunorubicin (daunomycin), liposomal daunorubicin, dexamethasone, docetaxel, doxorubicin, liposomal doxorubicin, epirubicin, estramustine phosphate, etoposide (VP-16-213), exemestane, floxuridine, 5-fluorouracil, fludarabine, fluoxymesterone, flutamide, gemcitabine, gemtuzmab, goserelin acetate, hydroxyurea, idarubicin, ifosfamide, imatmib mesylate, irinotecan, α-interferon, letrozole, leuprolide acetate, levamisole-HCl, lomustine, megestrol acetate, melphalan (L-phenylalanine mustard), 6-mercaptopurine, methotrexate, methoxsalen (8-MOP), mitomycin C, mitotane, mitoxantrone, nilutamide, nitrogen mustard (mechlorethamine hydrochloride), octreotide, paclitaxel, pegaspargase, pentostatin (2'-deoxycoformycin), plicamycin, porfimer, prednisone, procarbazine, rituximab, streptozotocin, tamoxifen, teniposide (VM-26), 6-thioguanine, thalidomide, thiotepa, topotecan, toremifene, trastuzumab, trimetrexate, vinblastine, vincristine and/or vinorelbine. The compounds of the invention can also be used together with immunomodulators or immunostimulators; preferred immunomodulators or immunostimulators are: propirimine, anti-human alpha-interferon antibodies, IL-2, GM-CSF, interferon-α, diethyl dithiocarbamate, tumor necrosis factor, naltrexone, tuscarasol, rEPO and antibiotics such as pentamidinisethionate, but also agents preventing or combating malignant tumors associated with viral diseases. In the method for the treatment of viral, bacterial, ~~fungicidal~~ mycotic and/or parasitic infections or of cancer, the compounds of the invention, as set forth above, can be administered together with tolerable carriers,

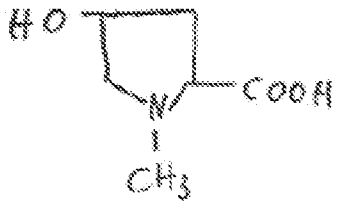
adjuvants or vehicles. Pharmaceutically tolerable carriers, adjuvants and vehicles which can be employed in the drugs of this invention include ion exchangers, aluminum oxide, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol-1000 succinate or other similar polymer delivery matrices, serum proteins such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acids, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamin sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silicon dioxide, magnesium trisilicate, polyvinylpyrrolidone, cellulose-based materials, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene block polymers, polyethylene glycol and wool fat, but are not restricted thereto. Cyclodextrins such as α-, β- and γ-cyclodextrins or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins or other solubilized derivatives can also be used with advantage to enhance the delivery of the compounds according to the invention. In the context with this method, the compounds of the invention can be administered orally, parenterally, via inhalation spray, topically, rectally, nasally, buccally, vaginally, or by means of an implanted reservoir. Oral administration or administration via injection is preferred as the form of contacting. The drugs of this invention may include any conventional non-toxic, pharmaceutically tolerable carriers, adjuvants or vehicles. In some cases, the pH value of the formulation can be adjusted by means of pharmaceutically tolerable acids, bases or buffers so as to increase the stability of the formulated compound or delivery form thereof. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion methods as a form of contacting. --

On page 35, between lines 3 and 4, please insert:

-- DESCRIPTION OF VARIOUS AND PREFERRED EMBODIMENTS OF THE INVENTION –

On page 36, starting on line 13:

-- Preparation of 4-hydroxy-1-methylproline (A-0-21)



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On page 50, please delete line 1 and insert therefore:

-- WHAT IS CLAIMED IS: --